REMARKS

Claims 90-178 are pending in the instant application. Claim 94 has been amended to recite that the anti-genedigit is RNA. Support for this amendment can be found in paragraph [024] and [030] of the publication of the application, US20030013091 A1. Claims 95-150, 153-156, and 158-178 have been amended to reinstate the claim dependencies that were inadvertently replaced with error codes in the response filed on February 7, 2007. The amendment obviates that informality noted in paragraph 4 on page 2 of the Office Action (it should be noted that claims 151-152 and 157 are independent claims which did not contain the error code that appeared in dependent claims). Claims 123, 130 and 131, which are multiply dependent claims, have been amended to indicate that the claim dependencies are in the alternative. This amendment obviates the objection to these claims noted in paragraph 6 on page 3 of the Office Action.

The specification has been amended to recite sequence identifiers for the sequences on pages 36 and 53 of the specification. This amendment, together with the sequence listing submitted herewith, obviates the objections to the specification set forth in paragraph 5 on page 2 of the specification.

The specification has also been amended to insert the sequence listing submitted herewith.

No new matter is introduced by the amendments made herein.

INTERVIEW SUMMARY RECORD

Applicant and Applicant's representatives thank Supervisory Patent Examiner Gary Benzion and Examiner Suryaprabha Chunduru for the courtesy of the telephonic interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicant presents this interview Summary Record of the interview of October 5, 2007 ("the Interview") between Supervisory Patent Examiner Gary Benzion, Examiner Suryaprabha Chunduru, and Drs. H. Perry Fell, Sherri Rogalski, Adriane M. Antler and Muna Abu-Shaar, in connection with the above-referenced application. During the Interview, the Office Action dated May 10, 2007 ("Office Action") was discussed.

During the Interview, Dr. Antler explained why prior art relied upon by the Examiner in the instant Office Action, U.S. Patent No. 6,261,779 B1 by Barbera-Guillem et al. ("Barbera-Guillem") and Tanke et al., 1999, European Journal of Human Genetics 7:2-11

("Tanke"), whether alone or in combination, did not make obvious the subject matter of the instant claims. Details of the arguments presented in support of patentability, are found hereinbelow.

THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The Present Claims

Claims 90-156 and 178 are directed to diverse populations of labels. The diverse populations of the invention have several "basic" features in common:

(1) the *populations comprise at least 30* (or, in claim 152, at least 100) *unique labels*, which as defined in the specification (see ¶ [0021] of US20030013091 A1) means that each unique label "has a detectable signal that distinguishes it from other labels in the same mixture." Thus, there are 30 or more labels in the population, each of the 30 or more labels giving rise to a signal that is distinguishable from the other 29 or more labels.

(2) wherein each of said *unique labels comprises a molecule, said molecule comprising a plurality of genedigits* (defined as "region of pre-determined nucleotide or amino acid sequence that serves as an attachment point for a label," see ¶ [0017] of US20030013091 A1), each genedigit being of predetermined sequence. It should be noted that the claims require that the at least two genedigits are in a single molecule.

(3) wherein *at least two* (or, in claim 152, at least four) of said *genedigits are each attached to a respective anti-genedigit* (defined as "a nucleotide or amino acid sequence or structure that binds specifically to the gene digit," see ¶ [0017] of US20030013091 A1), each said anti-genedigit being *attached to at least one label monomer*.

Thus, claims 90-156 and 178 provide for diverse populations of (*e.g.*, 30 or more) labels distinguishable by virtue of the attachment of label monomers to genedigits via the specific binding of anti-genedigits to which the label monomers are attached. The modular permutations of genedigit/anti-genedigit combinations gives rise to diverse populations of unique, *i.e.*, distinguishable, labels, starting even from a small number of label monomers. The diverse populations of labels can be attached to target-specific sequences to detect

analytes of interest. See, *e.g.*, US20030013091 A1 at ¶¶ [0028], [0029] and [0079] and Figure 1. Accordingly, each of the *30 or more* labels in the population are *distinguishable in signal* from the other 29 or more, each label has at least 2 genedigits that are in a *single molecule*, each of the at least 2 genedigits being attached to a label monomer via the anti-genedigits (which are attached to the label monomer).

Claims 157-177 are directed to labeling kits useful for generating the diverse populations of the invention.

The Present Rejection

Claims 90-178 are rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,261,779 B1 by Barbera-Guillem *et al.* ("Barbera-Guillem") and Tanke *et al.*, 1999, European Journal of Human Genetics 7:2-11 ("Tanke").

According to the Examiner, Barbera-Guillem teaches:

> ...a composition and kit... comprising a diverse population of unique labels comprising plurality of distinguishable labels (quantum dots having two or more unique labels) each unique label comprises a molecule (nanocrystal) said molecule comprising plurality of genedigits (polynucleotide strands (primary quantam (*sic*, quantum) dots), each genedigit being a predetermined sequence wherein genedigit is attached to an anti-genedigit (secondary quantum dots comprising complementary sequence to a polynucleotide on the primary quantum dot (see at least col. 2, line 13-46, col. 22, line 4-67, col. 23, line 1-33, col. 24, line 1-25).

Office Action at page 3. The Examiner also contends that Barbera-Guillem also teaches other aspects of the invention (Office Action at pages 4-5), but does not teach a diverse population of thirty or more labels "or label combinations" (Office Action at page 5).

The Examiner then goes on to say that:

> Tanke et al. teach multi-color fluorescence in-situ hybridization probes, wherein Tanke et al. teach that the combitorial (*sic*, combinatorial) ratio labeling result in unique labels with different distinguishable colors giving more that 30 unique labels or 48, 96 or more distinguishable colors or labels (see page 3, col. 2, paragraph 1, paragraph 1-2 under Materials and methods col. 1, paragraph 3 under introduction)" (Office Action at page 4).

The Examiner concludes that one of skill in the art would have been motivated

> to combine the diverse population of quantum dots comprising genedigits and anti genedigits as taught by Barbera-Guillem et al. with an inclusion of combitorial (*sic*, combinatorial) ratio labeling as taught by Tanke et al. to develop a sensitive and improved population

> of molecules with distinct labels. An ordinary artisan would have had a reasonable expectation of success that such modification of diverse population of quantum dots taught by Barbera-Guillem et al. in a manner as taught by Tanke et al. would result in a large population of unique labels because Tanke et al. explicitly taught that combitorial (*sic*, combinatorial) labeling or binary ratio labeling provides the number of recognizable targets (n) using (k) different fluorophores result in $n = 2^k - 1$ colors that utilizes no major instruments to analyse other than a good digital fluorescence microscope (see page 3, col. 1 paragraph 3, col. 2, paragraph 1, paragraphs 1-2 under materials and methods section) and such modification of the method is considered obvious over the cited prior art.

Office Action at pages 5-6.

The Examiner contends that the present claims are obvious over Barbera-Guillem in view of Tanke. Applicant submits that the Examiner's assessment of Barbera-Guillem and Tanke is in error, and the pending claims are not obvious over the references, as discussed below.

Barbera-Guillem and Tanke Do Not Render Obvious the Present Invention

Barbera-Guillem

Barbera-Guillem generally relates to detection of target nucleic acids using nanocrystals that are functionalized to be water-soluble, and further functionalized to comprise a plurality of polynucleotide strands of a known sequence which extend outwardly from each nanocrystal (see column 2, lines 13-19). According to the teachings of Barbera-Guillem:

> [A] basic principle of the invention is that a molecular probe is used to detect a target molecule, if present in a sample, by the binding specificity of the molecular probe for the target molecule or a portion thereof; and generation and amplification of a detectable signal by using at least two species of functionalized nanocrystals. A first species of functionalized nanocrystals ("primary dots") have extending therefrom strands of polynucleotides of known sequence, and wherein the primary dots are, or become, operably linked to the molecular probe. A second species of functionalized nanocrystals ("secondary dots") also have strands of polynucleotides of known sequence extending therefrom, wherein the nucleic acid sequence of the polynucleotide strands of the secondary dots is sufficiently complementary to the nucleic acid sequence of the polynucleotide strands on the primary dots such that, under suitable conditions for promoting contact and hybridization, the respective complementary strands hybridize to each other in forming a dendrimer.

Barbera-Guillem at column 2, lines 9-37. The signal generated by Barbera-Guillem is then *amplified* by "subsequent additions of functionalized nanocrystals [that] alternate between primary dots and secondary dots," which result in the formation of "a dendrimer of multiple layers of functionalized nanocrystals" (see column 2, lines 37-44). The resulting dendrimer is illustrated in Figure 3 of Barbera-Guillem, reproduced below (in which 1′ are primary dots and 2′ are secondary dots):

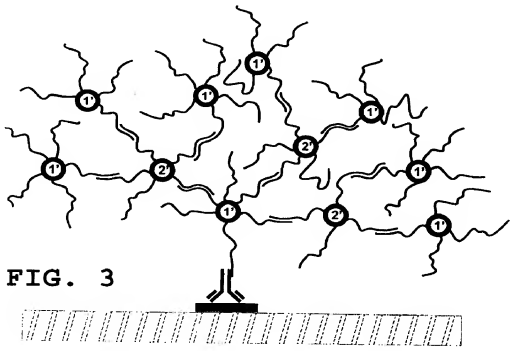

FIG. 3

Although Barbera-Guillem teaches "several variations of this system" (column 2, line 19), the variations mostly relate to the molecular probe which recognizes the target molecule (see, *e.g.*, Barbera-Guillem at column 9, line 11 through column 10, line 2, Figures 4 and 5 and Example 4 beginning at column 18); in the embodiment illustrated in Figure 3 above, the molecular probe is an antibody (illustrated bound to its target molecule) (column 2, line 66 through column 3, line 4). It should be noted, however, that in no embodiment is there more than one genedigit/anti-genedigit combination attached to any single molecule, in contrast to the labels of the presently claimed invention, each of which comprises a plurality of genedigits, at least two of which are attached to respective anti-genedigits.[1] Moreover, there is no suggestion, nor a common sense reason, to generate a molecular probe with a plurality

[1] During the Interview, Examiner Chunduru contended that each of Barbera-Guillem's dendrimers has multiple genedigit/anti-genedigit attachments. Dr. Antler noted that each oligonucleotide attached to a nanocrystal is a separate molecule, and, because no single oligonucleotide molecule that is attached to a nanocrystal hybridizes to more than one other complementary oligonucleotide molecule attached to another nanocrystal, there is no more than a single genedigit/anti-genedigit attachment in any one molecule.

of genedigits, at least two of which are attached to a respective anti-genedigit. *Cf. KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007).

Moreover, the goal of Barbara-Guillem is *to increase assay sensitivity* by amplification of a single signal: the result of the subsequent additions of functionalized nanocrystals is "*an exponential increase* in the amount of detectable signal that can be detected from a single molecular probe" (see column 2, lines 37-44) (emphasis added). Accordingly, Barbera-Guillem teaches that the quantum dots that are used are substantially uniform and give rise to "a discrete fluorescence peak" (column 10, lines 6-17). It is to be noted that in Figure 3 primary and secondary dots differ in the sequence attached thereto, not in the signal produced from the dot. Barbera-Guillem does discuss constructing unique dendrimers that emit distinguishable signals, to detect "more than one" target molecule, but the example given is of two different genes, and thus two distinguishable signals (see Barbera-Guillem at column 22), which is nowhere near the 30 distinguishable signals of the instant claims. In the embodiment describing the detection of two genes simultaneously, Barbera-Guillem notes that the presence and absence of each gene is "*detected simultaneously and distinctly*" as a result of "a color representative of the fluorescence emission generated by the functionalized nanocrystals of the first set, and a different color representative of the fluroescence emission generated by the functionalized nanocrystals of the second set, respectively" (Barbera-Guillem at column 22, lines 53-60)(*emphasis added*). Thus, since "multiplexing" in Barbera-Guillem relies on distinguishing different discrete fluorescence peaks, it is important to note that Barbera-Guillem does not teach 30 different nanocrystals that produce distinguishable signals, much less how one could distinguish the spectral peaks produced by 30 different dendrimer structures.

Accordingly, the disclosure of Barbera-Guillem does not make obvious the idea of generating a diversity of labels in the same population with both the distinguishable signals *and* basic structural features specified in the instant claims.

Therefore, Barbera-Guillem does not render obvious a population of thirty or more (as claimed in claims 90-94 and 151) or one hundred or more (as claimed in claim 152) unique labels, each comprising a molecule with a plurality of genedigits, in which at least two genedigits (or, in the case of claim 152, at least four genedigits) are each attached to a respective anti-genedigit, each anti-genedigit being attached to at least one label monomer, as specified by the claims. Nor does Barbera-Guillem even suggest how such a diverse

populations of 30 or more unique labels, *i.e.*, each distinguishable from the other 29 or more, can be achieved.

Thus, Barbera-Guillem does not render obvious the subject matter of any of independent claims 90-94, 151 and 152.

With respect to claim 157, Barbera-Guillem does not teach or suggest a labeling kit comprising in one container thirty or more unique molecules with a plurality of genedigits of predetermined sequence and in one or more other containers a plurality of respective anti-genedigits, each attached to at least one label monomer, for the same reasons as discussed above. Thus, Barbera-Guillem also does not teach or suggest the subject matter of independent claim 157.

For the foregoing reasons, the dependent claims are also nonobvious over Barbera-Guillem.

Tanke

Tanke does not remedy the deficiencies of Barbera-Guillem. Tanke is directed to multicolor *in situ* hybridization to detect chromosomal abnormalities (Tanke at Abstract) using the principle of "COBRA," i.e., COmbined Binary RAtio labelling, which is based on the simultaneous use of combinatorial labelling (using different, spectrally distinct fluorophores) and ratio labelling (using different combinations of different fluorophores in different ratios).

Although Tanke suggests the use of COBRA "to achieve a FISH multiplicity of 48, 96 or more" (Tanke at page 3, right column, second paragraph), that multiplicity is not suitable for, or adaptable to, the dendrimers of Barbera-Guillem, for the reasons discussed below.

First, as stated above, in Barbera-Guillem the goal is to amplify a single signal, or "a discrete fluorescence peak" (Barbera-Guillem at column 10, lines 16-17) and, where more than one signal is detected, the discrete signals arise from spectrally distinct fluorophores that are detected "simultaneously and distinctly" (Barbera-Guillem at column 22, line 56). In contrast, the COBRA method of Tanke uses different fluorophores in different ratios to label chromosomes, and measures different combinations and ratios of fluorophores present at different "segments" of chromosomes, *i.e.*, at spatially discrete locations on a solid phase (Tanke at page 6, right column).

Given Barbera-Guillem's goal of signal amplification of a "discrete fluorescence peak," Tanke's use of different different fluorophores in different ratios is incompatible with Barbera-Guillem's signal amplification goal, and thus there is no common sense reason to modify the dendrimer structure described by Barbera-Guillem with Tanke's COBRA system, even if that modification were possible. *Cf. KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007). Indeed, such a modification, using multiple fluorophores in different ratios, would not enhance and might obscure Barbera-Guillem's single peak, and would thus render the Barbera-Guillem dendrimer structure unsatisfactory for its intended purpose. Accordingly the modification is non-obvious. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

Moreover, it should be noted that Tanke's multiple labels are incompatible with Barbera-Guillem's form of multiplexing. In particular, and as discussed above, multiplexing according to Barbera-Guillem requires the use of dendrimers containing spectrally distinct nanocrystals, *i.e.*, nanocrystals with distinct spectral emissions so that the dendrimers complexed to different target molecules can be detected simultaneously and distinguished from one another by virtue of the distinct spectral emissions (see Barbera-Guillem at column 22, lines 44-46). In other words, for each gene to be detected by Barbera-Guillem's method, a binary "yes" or "no" decision is made based on the presence/absence of each fluorescence peak. However, as Tanke notes, generating labels for multiplexing by using combinations of spectrally distinct fluorophores is limited and thus only 27 different labels had been reported, using five distinct fluorophores (Tanke at page 3, left column, 3rd paragraph). Thus, for example, Tanke mentions that "the available spectrum for five fluorophores is already utilized from the UV to the near infra-red," and thus "introduction of a sixth dye may lead to increased spectral overlap and undesirable cross talk between detection channels" (Tanke at page 3, left column, 4th paragraph).

Accordingly, to facilitate detection of a greater number of targets, Tanke developed the COBRA method which utilizes ratio labeling, "by which a given probe is composed of a mixture of probes with different fluorescent labels" to generate additional "recognizable colours," in combination with a binary label (Tanke at page 3, right column, 1st paragraph).

Although this method is useful for chromosome labeling, because the fluorophore ratio for each spatially distinct chromosome segment can be assessed separately due to the spatial separation on a solid phase, as explained on page 3, right column of Tanke, "ratio labelling is more complex than combinatorial labelling. Recognition of chromosomes stained

with ratio labelled probes is not a 'yes or no' colour decision...but requires accurate measurement of colour." The probes in Tanke comprise mixtures of the same probe, differently labeled. Among the labels generated by Tanke, at least some of the probes forming a distinguishable label have differing amounts of the same fluorophore(s) present in the probes forming other labels. In other words, the fluorophores in Tanke's different labels are not spectrally distinct but require accurate measurement of the emission amounts of the fluorophores therein at discrete physical locations. Thus, in order to distinguish one ratio labeled probe from another, Tanke relies on the spatial separation of the probes afforded by their binding to different chromosomes.[2]

If the ratio labeled probes of Tanke, which are not spectrally distinct, were to be somehow attached to the dendrimers of Barbera-Guillem, the dendrimers would not be usable in Barbera-Guillem's multiplexing method, because dendrimers attached to different targets would not be spectrally distinguishable. Accordingly, this is yet another reason for which modification of the dendrimer structure described by Barbera-Guillem with Tanke's COBRA system, even if it were possible, does not make sense. *Cf. KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007). As explained above, such a modification, involving the attachment of Tanke's ratio labeled probes to Barbera-Guillem's dendrimers would render the dendrimers unsatisfactory for their intended purpose. Accordingly the modification is non-obvious. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

Moreover, even assuming, *arguendo*, that the modification of the dendrimers of Barbera-Guillem with Tanke's COBRA were desirable, it is unclear how that could be achieved, since the Barbera-Guillem dendrimers contain multiple layers of oligonucleotide-bound nanocrystals, whereas Tanke's COBRA probes are DNA probes that recognize the target DNA and that are randomly labelled by, *e.g.*, chemical labeling or nick translation (page 3, right column, first paragraph under the "Materials and Methods" heading; page 4, right column, first paragraph under the "Multicolour FISH Staining of Human Chromosomes" heading). It is unclear how such labelled probes could be used to form Barbera-Guillem's dendrimer structures. Moreover, even if such labelled probes could be used, it is unclear how Barbera-Guillem's dendrimer structures can be formed in a manner that would preserve the precise ratios of the different fluorophores as taught by Tanke. In

[2] In particular, in Tanke, individual chromosomes are primarily classified according to their color values in the color triangles of Figure 1, representing the different ratio labels (see Tanke at page 7, left column), and also the length of the chromosome (see Tanke at page 7, right column).

addition, while the signal in Barbera-Guillem's probes is emitted by the nanocrystals to which oligonucleotides of a preferred length of 6-50, more preferably 10-20, nucleotides (Barbera-Guillem at column 14, lines 31-36), probes used in chromosome painting range from 200 to 600 nucleotides in length (see Genome Analysis : A Laboratory Manual: Mapping Genome (Genome Analysis Series, Vol. 4), Bruce and Birren, eds. (1998)) (submitted as reference C01 of the Information Disclosure Statement submitted concurrently herewith). It is unclear whether or how the longer probes suitable for chromosome painting methods such as Tanke's can be utilized in Barbera-Guillem's dendrimers.

Finally, it should be noted that Tanke does not suggest other aspects of claims 90-94. For example, Tanke describes a method of chromosome FISH, which is performed on a solid surface, such as a slide, and thus does not suggest a population in solution, as claimed in claim 90. This is shown by Tanke at page 5, second column under the heading "FISH Staining of Human Metaphase Chromosomes," which discusses the "[s]lides with metaphase chromosomes."

Tanke also does not suggest more than two components of any chromosome-probe complexes: the chromosome and the corresponding probes. In contrast, claims 91 and 92, recite at least three components: the molecule comprising genedigits, at least two anti-genedigits (each attached to a label monomer), and either a bound target molecule (claim 91) or a bridging nucleic acid (claim 92).

Yet further, Tanke does not suggest a synthetic nucleic acid, as claimed in claim 93, since chromosomal DNA is not synthetic, nor the use of an anti-genedigit that is RNA, as recited by amended claim 94.

In view of the foregoing, Applicant submits that the rejection under 35 U.S.C. § 103 is in error and should be withdrawn.

CONCLUSION

Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

Respectfully submitted,

Date: November 13, 2007

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